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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/787,292 | 03/15/2001 | Yoshimi Homma | 31671-169944 | 7573 |

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VENABLE, BAETJER, HOWARD AND CIVILETTI, LLP
P.O. BOX 34385
WASHINGTON, DC 20043-9998

| EXAMINER | |
|---|---|
| GOLDBERG, JEANINE ANNE | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1634 | |

DATE MAILED: 03/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/787,292 | HOMMA ET AL. | |
| | Examiner | Art Unit | |
| | Jeanine A Goldberg | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *December 3, 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 5-29* is/are pending in the application.

4a) Of the above claim(s) *9-14 and 17-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-8, 15-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0103* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. This action is in response to the papers filed December 3, 2003. Currently, claims 1, 5-29are pending. Claims 9-14, 17-29 have been withdrawn as drawn to non-elected subject matter.

2. Any objections and rejections not reiterated below are hereby withdrawn in view of applicant's amendments to the claims and arguments.

### *Election/Restrictions*

3. Applicant's election without traverse of Group I in Paper No. 12 is acknowledged. Claims 9-14, 17-29 are withdrawn from consideration.

The requirement is still deemed proper and is therefore made FINAL.

### *Priority*

4. This application claims priority to 371 Application PCT/JP99/05069, filed September 17, 1999. The application also claims priority to foreign application 10-265089, filed September 18, 1998.

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

***Claim Rejections - 35 USC § 112-Scope of Enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 5-8, 15-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting a predisposition to psoriasis which comprises determining the methyolation of cytosine residues as positions 668, 671, 687, 697 of SEQ ID NO: 4 wherein the presence of less than one methylated cytosine is indicative of a predisposition to psorisasis, does not reasonably provide enablement for a method of diagnosis psoriasis by determining the mehtylation of cytosine residues at the specific region of the epidermal growth factor receptor and detecting a psoriasis patient whose sample's genomic DNA has less cytosine residues than a healthy person's genomic DNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a method of diagnosising psoriasis by determining the mehtylation of cytosine residues at the specific region of the epidermal growth factor receptor and detecting a psoriasis patient whose sample's genomic DNA has less cytosine residues than a healthy person's genomic DNA.

The specification provides a single example which analyzes 30 normal patients and 30 patients with psoriasis for cytosine methylation at positions 668, 671, 687, 697 of SEQ ID NO: 4. The example uses sodium bisulfite treatment of genomic DNA to detect methylation in the promoter region of EGF-R gene from nucleotides 384-962 of SEQ ID NO: 4 (page 10, paragraph number 4). The genomic DNA, following bisulfite treatment was altered such that methylated cytosine residues are protected and unmethylated cytosine residues are alerted to become thymine residues by PCR amplifications. It is only with the bisulfite treatment that the cytosines which are unmethylated are detected. The specification teaches the analysis of four specific methylated cytosines. These cytosines are all located within the promoter region of the EGF-R gene. As provided in Table 1 and Figure 1, the results of the methylation analysis are provided. The data appears to illustrate that individuals with psoriasis have less than 1 methylated residue (73%) as compared to healthy patients with less than 1 methylated cytosine (3%). Therefore, the data suggests that individuals with less than 1 methyalted cytosine are likely to be at an increased risk or predisposition to psoriasis. As seen in Figure 1, several healthy individuals have less cytosines than psoriasis patients. Thus, based

solely on the number of methylation, the skilled artisan would be unable to reliably diagnose psoriasis. With respect to the analysis of –446 (668 of SEQ ID NO: 4), the specification teaches that the residue is methylated in 5 patients with psoriasis and 20 normal individuals. The specification teaches that the probability for mistake is about 33%. Thus, this does not seem statistically significant given the high degree of error.

The art teaches methyaltion in the EGFR gene. Gnmou discloses a method for determining the methylation level of cytosine residues of the regulatory region of the EGFR gene in samples taken four different types of lung carcinoma (page 990, left column, second paragraph through page 991 , right column). Gamou further discloses the use of the methylation sensitive restriction enzyme Hpa 11 (page 990, right column).

Similarly, Kaneko teaches the methylation status of EGFR gene promoter in human hepatocellular carcinoma.

Neither the specification nor the art teach the skilled artisan how to make and use the claimed invention as broadly as claimed. First, the claims are broadly drawn to detecting methylation in the entire EGFR gene. However, the specification and the art only provide teachings that suggest that the promoter contains methylation. While one could conduct additional experimentation to determine whether, e.g., additional methylated sites occur within the EGFR gene and whether these additional sites are associated with psoriasis, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue. The teachings of the specification do not establish that one could actually detect the absence of methylated cytosines throughout the EGFR gene as an indicator of psoriasis. Rather

the teachings in the specification assert four specific methylated sites in the promoter region which are hypomethylated in psoriasis patients. In the absence of guidance from the specification, one skill in the art may look to the teachings of the prior art for enablement of a claimed invention. However, the closes prior art references, namely Gamou and Kaneko, do not provide support for the use of methylation as an indicative of psoriasis. Thus, it is unpredictable as to whether one could successfully use the claimed invention, and given the fact that neither the specificication nor the prior art provide evidence of a correlation between methylated cytosines throughout the EGFR gene and psoriasis, it is further unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention. Accordingly, it would require undue experimentation for a skilled artisan to use the claimed invention.

Moreover, as written the claims are directed to methods of diagnosis. The data in the specification and the art does not support a method for diagnosis based upon the detecting of cytosines. Unless the genomic DNA had been treated with bisultite to alter the nucleotide sequence following amplification, the number of cytosines would be the same. Moreover, the data in the Table and Figure illustrate that several normal individuals have less cytosines than psoriasis patients. Therefore, without further experimentation, the diagnosis of psoriasis based upon number of methylated cytosines would be unpredictable. The data appears to support a predisposition, however since the specification states that there is a 33% chance for mistake for detecting methylation at position 668, this is not sufficient to enable a diagnosis claim.

With respect to Claim 15, the claim is drawn to a method of detecting the methylation of cytosine residues involved in the expression EGFR gene isolated sampling-blood. First, as noted below, the claim does not appear to provide any positive process steps for the method. Additionally, the specification fails to describe the "specific region of DNA involved in expression of EGFR." The skilled artisan would be required to perform additional experimentation to determine the region associated with expression of the gene. Furthermore, even when alterations in the methylation level of a receptor gene are demonstrated, these changes do not necessarily correlate to a change in the expression of the receptor. Gamou et al., Japanese Journal of Cancer Research 79:989-995, 1988 (hereinafter referred to as Gamou analyzed the methylation status of the epidermal growth factor receptor(EGFR) gene in five cell lines: two small cell lung carcinoma lines, two squamous cell carcinoma lines, and one adenocarcinoma line. Gamou found that Gtthe 5' region is methylation- 'free regardless of the expression status of the EGFR gene" and that ççgene methylation is not solely responsible for control of EGFR gene expression" (page 994, right column, lines 24-2%. Therefore, neither the specification nor the art has provided any direction to the specific region of DNA involved in the expression of EGFR.

***Claim Rejections - 35 USC § 112- Second Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim1, 5-8, 15-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1, 5-8, 15-16 are indefinite over the recitation "the specific region of epidermal growth factor receptor" because "the specific region" lacks proper antecedent basis. The claims does not clearly point out "the specific region" within the EGFR gene. Therefore, the metes and bounds of the claimed invention are unclear.

B) Claims 1, 5-8, 16 are indefinite over the recitation "detecting a psoriasis patient whose sample's genomic DNA has less cytosine residues than healthy person's genomic DNA." It is unclear how this step is intended flow from the previous step of detecting methylation. The method may have been intended to recite detecting the presence of methylated cytosines, rather than just cytosines. The number of cytosines in the patient and the healthy individual are the same, however, it appears based upon the specification, that the number of methylated cytosines may differ between patients and normals.

C) Claims 1, 5-8, 15-16 are indefinite because they appear to contain grammatical mistakes which render the claim indefinite. For example, Claim 1, step 1 is directed to "collecting a genomic DNA from each sample of psoriasis patients." It is unclear whether the claim should read collecting a genomic DNA sample from a person suspected of having psoriasis. Otherwise the claim samples DNA from individuals know to have psoriasis to detect psoriasis. This method does not appear to make sense. Moreover, step 2 requires "amplifying the gnomic DNA by using primers in accordance

with PCR method." It is unclear whether the claim is specifically referring to a PCR method or whether the claim is drawn to any PCR method. The claim could be amended for clarity to read, "amplifying the genomic DNA using primers in accordance with a PCR method." Finally, as discussed above, the final step is directed to detecting a psoriasis patient however, if the genomic DNA was taken from a psoriasis patient, the patient has already been identified.

D) Claim 15 lacks any positive process steps. Claims 15-16 are indefinite because the claims do not recite the basic steps of the claimed invention in a positive, active fashion (see Ex parte Erlich 3 USPQ2d, 1011). The claims describe a method for detecting the methylation of cytosine residues..., but the claims fail to recite any actual steps that define the method. Therefore, the metes and bounds of the claim are indefinite.

***Allowable Subject Matter***

7. The art does not teach nor fairly suggest an association between psoriasis and methylation status at positions 668, 671, 687, 697 of SEQ ID NO: 4. The specification teaches that the probability of mistaking a healthy person for a patient with psoriasis is less than 3% when analyzing each of positions 668, 671, 687, 697 of SEQ ID NO: 4 and detecting one or less methylated cytosines. A claim drawn specifically to:

A method of detecting a predisposition of an individual for developing psoriasis comprising: a) collecting genomic DNA from a patient suspected of having psoriasis

b) amplifying the genomic DNA using primers

c) determining the methylation of cytosine residues in epidermal growth factor receptor at positions 668, 671, 687, 697 of SEQ ID NO: 4

wherein the presence of less than one methylated cytosine is indicative of the individual to a predispostion to psoriasis.

***Conclusion***

**8. No claims allowable.**

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg
Jeanine Goldberg
March 18, 2003

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600